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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/121,798	07/23/98	BRIDENBAUGH	R 018484-00120

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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev 11/00)

Office Action Summary	Application No. 09/121,798	Applicant(s) Bridenbaugh et al
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Mar 20, 2001* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. Applicant's arguments with respect to claims 1-20 have been considered but are moot in view of the new ground(s) of rejection. Where the arguments apply to the references used in the new grounds of rejection, a response has been included in the new rejection below.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 18-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,011,148. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only substantial differences between the claimed invention and that disclosed by US Pat. No. 6,011,148 is the use of static mixers in the plasmid isolation prior to the use of ultrafiltration and or anion exchange chromatography in a plasmid procedure that can be readily automated.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 14-16 are drawn to the simultaneous performance of steps (a)-(d), (a)-(e) and (a)-(f) respectively. It is not clear from the claims or text of the specification how one of skill in the art would carry out a mixing step in a flow through mixer, a centrifugation step and a neutralization step simultaneously. It would appear that the steps are mutually exclusive, and each step would require separate equipment which would be difficult if not impossible to combine for the simultaneous performance of all three steps.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 517,515 A2 in view of US 6,197,553 B1 (of record), US 5,837,529 (of record) and Song et al.

The claims are drawn to a method for purifying at least about 100 mg. of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent in a static mixer, then adding a precipitation agent in a second static mixer, removing the precipitated component by centrifugation, neutralizing the solution, and passing the clarified solution over an ion exchange column. An ultrafiltration step may be performed before the ion exchange step.

EP 517,515 A2 taught (see the entire patent application) a method for purifying large quantities of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent, then adding a precipitation agent, removing the precipitated component by filtration followed by an ultrafiltration step. EP 517,515 A2 discusses the obvious and well known use of Rnase digestion and potassium acetate in the process.

EP 5,157,515 A2 did not teach a centrifugation step, a neutralizing step, or an ion exchange column step.

US 6,197,553 B1 taught (see especially the abstract and columns 1-6) the purification of large quantities of plasmid for pharmaceutical use by a heat lysis step in a flow-through heat

exchanger, followed by a centrifugation step, followed by a filtration step, followed by an ultrafiltration step, followed by an ion exchange step. The specific flow rates cited in the claims are merely optimizations of the method and are not patentably distinct.

US 5,837,529 taught (see especially the abstract, figures and columns 2-4) a method for purifying large quantities of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent in a static mixer, then adding a precipitation agent in a second static mixer.

Song et al. taught (see especially the abstract, introduction, page 3390, column 2, bottom, figures 1-4, page 3394, column 1, top, and the discussion at page 3396, column 2) the general theory of concentration polarization on a membrane during ultrafiltration. Song explains that the process of ultrafiltration involves the development of a polarization layer of the solute (in the instant claimed invention, the solute is the plasmid and other cell lysate products being purified, diafiltered and concentrated) on the ultrafiltration membrane, which provides a resistance to flow through the ultrafilter. The presence of this layer on the ultrafilter provides a "packed" layer of solute, or "gel layer", through which all other solute present in the solution must pass or else will be retained in the solution. This "gel layer" of "packed" solute on the ultrafilter provides a second layer for filtration, as discussed by Song et al. in the introduction, at page 3390, column 2, bottom, further demonstrated in figures 1 and 2, and then at page 3394, column 1, top. The practical aspects of managing a gel layer in ultrafiltration is a consideration of solute concentration versus pressure which controls the amount of gel layer formed on the ultrafilter.

The presence of "gel layer" on an ultrafiltration membrane is therefore an inherent aspect of ultrafiltration, and the physical retention of solute in an ultrafiltration process will always involve the development and management of the "gel layer".

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the method for purifying large quantities of plasmid DNA for pharmaceutical use of EP 517,515 A2 with the method for purifying large quantities of plasmid DNA for pharmaceutical use of US 6,197,553 B1 and US 5,837,529 because they were all involved in the process of purifying large quantities of plasmid DNA for pharmaceutical use. Song et al. provides the theoretical background on the formation of a "gel layer" in an ultrafiltration process.

One of ordinary skill in the art would have been motivated to combine the method for purifying large quantities of plasmid DNA for pharmaceutical use of EP 517,515 A2 with the method for purifying large quantities of plasmid DNA for pharmaceutical use of US 6,197,553 B1 and US 5,837,529 because EP 517,515 A2 taught (see column 2, lines 25-37) that the alkaline lysis method of bacterial cell lysis may be used as an equivalent to the heat lysis method of US 6,197,553 B1. US 6,197,553 B1 recites at column 2, lines 39-42 "recent advances in the field of polynucleotide-based vaccines for human use, and potentially human gene therapy, requires the ability to produce large quantities of the polynucleotide vaccine in purified form". Then at column 4, lines 43-56 state "preparative scale chromatography is a powerful purification tool that provides high resolution, operational ease and increased productivity for purifying DNA plasmid

products....chromatography steps achieve separations between various forms of plasmid (supercoiled, open, relaxed, linear and concatemers) and remove host contaminants like LPS (endotoxin), RNA DNA and residual proteins". US 5,837,529 states at column 2, bottom, bridging to column 3, top that the static mixers provide a distinct advantage for lysing large quantities of bacterial cells for the production of plasmids over other methods. Song et al. provides the theoretical background on the formation of a "gel layer" in an ultrafiltration process. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of EP 517,515 A2 with US 6,197,553 B1, US 5,837,529 and Song et al.

Response to Arguments

9. Arguments presented in Paper No. 16, filed March 20, 2001 assert that US 6,197,553 does not teach the alkaline lysis step of the instant claimed invention and that US 6,197,553 seems to teach away from the alkaline lysis step. EP 517,515 A2 provides the teaching that the heat lysis step of US 6,197,553 is equivalent to the alkaline lysis step of EP 517,553. US 6,197,553 teaches away from an alkaline lysis step which involves the use of materials in the step which would be toxic to the ultimate human consumer. EP 517,553 teaches an alkaline lysis step which does not employ the toxic materials and therefore, the objections to an alkaline lysis step which appear to "teach away" are moot.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

10. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is clearly stated in the rejection above where each of the references of US 6,917,553 and US 5,837,529 recite that the additional steps which they teach are advantageous for the process of purifying large scale plasmid DNA preparations for pharmaceutical use and their combination is therefore obvious.

Conclusion

11. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61

(November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

March 31, 2001

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